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EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/622,703	HOEFFLER, WARREN	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-14 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The allowability of claims 1-14 is withdrawn. As indicated in the letter of April 22, 2004, prosecution in this application is being re-opened. Upon further consideration, the following grounds of rejection are being applied. This action is made non-final.

Priority

2. If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For example, the first line of the specification should be amended to read: "This application is the National Stage of International Application PCT/US99/23277, filed October 6, 1999, which claims the benefit of U.S. Provisional Application 60/103,803, filed October 9, 1998.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for general methods for detecting the presence of single-stranded nicks in a DNA template and methods for introducing a nick into a DNA template wherein the method comprises providing a DNA template comprising at least one transcription factor, contacting the DNA template with said transcription factor and detecting the presence or absence of a nick in the DNA template wherein said transcription factor is CREB, TFIIIC or c-Jun/BPV-E2 , does not reasonably provide

enablement for a method for detecting transcription activity comprising detecting the presence of a nick in a DNA molecule as indicative of transcription activity or methods for detecting transcription activity by contacting a DNA template with any transcription factor and detecting the presence of a nick as indicative of transcription activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 1-9 are drawn to a method for detecting transcription activity comprising detecting the presence of a nick in a DNA molecule as indicative of transcription activity. Claims 10-14 are drawn to methods for detecting transcription activity comprising contacting a DNA template with a transcription factor and detecting the presence of a nick in the DNA template as indicative of transcription activity. The specification is not enabling for the claims as broadly written for the following reasons:

1) The specification (pages 12-17) teaches that the transcription factors CREB, TFIIIC and c-Jun/BPV-E2 bind to DNA templates and introduce a single-strand break in the vicinity of their DNA binding sites, thereby allowing RNA polymerase to access the

DNA template. The ability of these transcription factors to introduce nicks in the template DNA is associated with an increase in the rate of transcription. However, there are many additional mechanisms/activities which occur in vitro and in situ which lead to the introduction of single-stranded breaks/nicks in DNA molecules. For instance, exposure to X-ray and gamma-ray radiation results in the formation of single-stranded nicks in DNA molecules. Additionally, exposure to chemical carcinogens, oxidative stress and some topoisomerases are known to cause nicks in DNA molecules (see, EP 0628817A1, cited in the IDS of 8/21/00). Accordingly, the presence of a nick in a DNA molecule does not per se indicate that transcription has occurred or will occur at the site of the nick. The specification has not provided any particular means for distinguishing between nicks that are introduced by transcription factors and which are associated with transcription sites and nicks that are the result of other chemical or physical factors. Depending on the conditions of the assay and the types of DNA molecules being analyzed (i.e., source of DNA, type of isolation technique, in vitro vs. in vivo assay), it is expected that the majority of nicks in a DNA molecule would be the result of factors outside of those associated with transcription. In the absence of a specific correlation between nicks and transcription activity and in the absence of a specific means for distinguishing between nicks caused by transcription factors and nicks caused by other chemical and physical factors, it would be highly unpredictable as to whether a nick was associated with the occurrence of transcription activity or with the occurrence of another chemical or physical event. Undue experimentation would be required to practice a method which relies solely on the detection of a nick as a means for detecting

transcription factors since the specification does not provide any specific guidance as to how to distinguish by nicks caused by transcription factors versus nicks caused by other chemical and physical events. Accordingly, the specification has not enabled methods for detecting transcription activity wherein the methods comprise a single step of detecting the presence of a nick wherein the presence of a nick indicates transcription activity.

2) The specification has identified only 3 transcription factors, namely CREB, TFIIIC and c-Jun/BPV-E2, that bind to a DNA template and introduce a nick at or near the transcription factor binding site. The specification (pages 8-9) defines a transcription factor as including any effector molecule that links second messenger pathways to gene expression pathways allowing a range of cellular responses to extracellar stimuli. Based on the general knowledge in the art and in consideration of the functional activity of transcription factors, it is expected that only a subset of such transcription factors would have the property of binding to and introducing a nick in a DNA molecule. Given the disclosure of only 3 transcription factors which introduce nicks into DNA and in view of the breadth of molecules encompassed by "transcription factors," the specification has not taught a representative molecules within the claimed genus which could be used to perform a method of detecting transcription activity by assaying for the presence of a nick in a DNA molecule. The specification (page 5) states that the invention is inclusive of methods for identifying additional transcription factors and their binding sites utilizing a DNA nicking assay. However, such assays are performed only as a means of conducting additional research. Providing methods of searching for additional

transcription factors useful within the claimed invention is not equivalent to providing specific transcription factors that can be used to introduce nicks into DNA templates as a means for analyzing transcriptional activity. It is unpredictable as to what types of additional transcription factors would be capable of introducing nicks into DNA templates. The specification has not provided any information regarding a relationship between the structure and function of transcription factors that are capable of nicking DNA at sites at which transcription is to be initiated. In the absence of a clear structure-function relationship, one cannot readily envision additional transcription factors that are can be used in the claimed invention. Additional transcription factors can only be identified through random, trial and error experimentation involving assaying each of the possible transcription factors to determine whether they possess DNA nicking activity. Such random experimentation is considered to be undue.

Accordingly, in view of the unpredictability in the art and the lack of specific guidance provided in the specification, undue experimentation would be required to practice the invention as it is broadly claimed.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-14 are indefinite over the recitation of "detecting transcription activity." This phrase is not clearly defined in the specification and there is no art recognized

definition for this phrase which would allow one to determine the meets and bounds of this phrase within the present claims. It is unclear as to whether methods "of detecting transcription activity" refers to methods which detect whether transcription has occurred, is in the process of occurring, will occur or has the potential to occur. Claims 1-9 recite only a step of detecting the presence of a nick in a DNA molecule. The claims do not recite any additional limitations which are reflective of the steps involved in transcription. While the specification indicates that the transcription factors CREB, TFIIIC and c-Jun/BPV-E2 introduce a nick into a DNA molecule, nicking is also caused by other chemical and physical factors. Thereby, it is unclear as to how detecting the presence of a nick results in the detection of transcription activity and thus it is unclear as to what is intended to be encompassed by detecting transcription activity. Similarly, claims 10-14 are indefinite. While claims 10-14 further include the step of contacting a DNA template with at least one transcription factor, the claims do not clarify how the contacting step and detection of a nick result in the detection of transcription activity.

Claim 12 is indefinite over the recitation of "wherein the DNA template is inserted into a viral or plasmid vector and introduced into a cell." It is not clear as to whether this phrase is intended to constitute an active process step (i.e., wherein the method further comprises, prior to step a, inserting the DNA template into a viral or plasmid vector and introducing the resulting recombinant plasmid or vector into a cell), or whether this recitation is intended only to further define the DNA template. In the later case, it is unclear as to how this recitation further limits the claim. Since the claim does not require isolating the DNA template by any particular means, it is unclear as to how the fact that

the DNA template was originally present in a cell further modifies the method or further characterizes the DNA template. It is also unclear as to whether the DNA template set forth in step (a) is provided in a viral or plasmid vector or whether the claim includes providing any type of DNA template.

Similarly, claims 13 and 14 are indefinite over the recitation of "is fixed to a matrix." It is unclear as to whether the claims include a step of fixing a DNA template to a matrix or whether the claims require that in any one of (or all of) steps a, b and c, the use of a DNA template fixed to a matrix.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Komatsu (Toxicology and Industrial Health (1991) 7: 5/6, pages 495-497).

Komatsu teaches a method for detecting transcriptional activity wherein the method comprises detecting the presence of a nick in a DNA molecule, wherein the presence of a nick indicates transcriptional activity. Komatsu teaches that the presence of a nick is detected using a nick translation assay. This assay is considered to be a primer extension reaction since the assay involves the extension of nucleic acids using dNTPs and DNA polymerase. Komatsu teaches that "the in situ nick translation method is effective in analyzing transcriptionally active and inactive chromatin" (see abstract).

The reference (page 496) states that "(t)his method is important as a rapid means for detecting the interaction between chemical carcinogen and genes able to be transcriptionally activated." Accordingly, the claimed invention is anticipated by the method of Komatsu.

6. Claims 1, 2, 6, 7, 10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Gansz (Molecular Gen Genetics (1991) 225: 427-434).

Gansz teaches methods for analyzing transcriptional activity. The reference teaches that binding of the DsbA transcription factor to double-stranded DNA enhances transcription activity. At page 428, Gansz states that "binding of the protein is accompanied by nicking of the DNA. These nicks might contribute to activation of the template for late transcription." Gansz (page 432) also teaches methods for detecting the presence of a nick in a DNA template wherein the methods comprise providing a DNA template, contacting the template with DsbA protein, and separating the products electrophoretically on a sequencing gel. An autoradiogram was used to reveal the presence of specific nick sites within the DNA template. The reference also teaches methods for detecting the presence of transcription activity resulting from the binding of DsbA to the DNA template. The method steps set forth by Gansz are identical to those set forth in the present claims. That is, Gansz teaches methods for detecting transcription activity wherein the methods include the step of detecting the presence of a nick in a DNA molecule. The present claims do not recite any additional steps or limitations which result in a manipulative difference between the claimed method and the method disclosed by Gansz.

With respect to claim 6, Gansz also teaches that the reaction products were separated on a sequencing gel and Gansz teaches the locations of the nick sites. Thereby, Gansz teaches the detection of nicks using a sequencing assay. With respect to claim 7, Gansz teaches detecting the presence of a nick in a DNA molecule using a footprinting assay (page 432) and thereby teaches detecting the presence of a nick by a "protein binding assay." With respect to claim 12, Gansz (page 432) teaches detecting the presence of a nick in a DNA template that is provided in a plasmid vector. It is noted that the recitation of "is introduced into a cell" does not distinguish the claimed method over that of Gansz since the claim does not require performing a step of introducing a plasmid into a cell and the plasmid provided by Gansz was isolated from a cell (see page 428).

RESPONSE TO ARGUMENTS:

In the Brief filed, August 8, 2003, Applicant traversed the previous grounds of rejection. Applicant argued that Gansz does not teach that nicking is predictive of transcriptional activity. Applicants point out that Gansz states that the presence of nicks was surprising and that the authors were unable to provide an explanation for their results. Applicants arguments have been fully considered but are not persuasive to overcome the present grounds of rejection. The claimed method requires only the detection of a nick (and, with respect to claim 14,contacting a DNA template with a transcription factor). The claims state that the detection of the presence of a nick indicates transcription activity. Since the method of Gansz includes the same method steps, the method of Gansz would also necessarily result

in the same conclusion, i.e., that the presence of a nick indicates transcription activity. Applicants further argue that the method of Gansz was not performed under conditions that would "allow for actual transcription to take place, (i.e., no additional transcription factors, polymerases, nucleoside bases, etc)." This argument is not convincing because the present claims also do not require any steps which would indicate that transcription occurs. Rather, the claims require only contacting a DNA molecule with a transcription factor and detecting the presence of a nick. Since the method of Gansz involves the same steps, i.e., contacting a DNA molecule with the transcription factor dsbA and detecting the presence of a nick in said DNA molecule, the method of Gansz would also necessarily be one in which the presence of a nick indicates transcription activity. The recitation in the preamble of a "method of detecting transcription activity" does not result in a manipulative difference in the method steps and does not distinguish the claimed method over that of Gansz.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gansz in view of Brown (U.S. Patent No. 5,612,180)

Gansz teaches methods for analyzing transcriptional activity. The reference teaches that binding of the DsbA transcription factor to double-stranded DNA enhances transcription activity. At page 428, Gansz states that "binding of the protein is accompanied by nicking of the DNA. These nicks might contribute to activation of the template for late transcription." Gansz (page 432) also teaches footprinting methods for detecting the presence of a nick in a DNA template wherein the methods comprise providing a DNA template, contacting the template with DsbA protein, and separating the products electrophoretically on a sequencing gel. An autoradiogram was used to reveal the presence of specific nick sites within the DNA template. In the footprinting methods, DNase I is added to control reactions, while no DNase I is added in reactions that assay for DsbA nicking. The reference also teaches methods for detecting the presence of transcription activity resulting from the binding of DsbA to the DNA template. Gansz does not teach detecting DNA nicking using an S1 nuclease assay or a method which involves primer extension or PCR.

However, Brown teaches alternative methods for performing footprinting methods and teaches that nicks can be introduced into DNA using S1 nuclease (see, for example, column 6). Brown also teaches amplifying the DNA molecule used for footprinting using the method of PCR, which is considered to be a "primer extension reaction."

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Gansz so as to have used S1 nuclease in place of DNase I because Brown teaches that S1 nuclease is an equally effective enzyme for nicking DNA and thereby would have provided an equally effective enzyme for analyzing the binding and nicking activity of DsbA. Additionally, with respect to claims 4 and 5, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Gansz so as to have amplified the DNA template by PCR as part of the assay to detect the presence of a nick in order to have provided a sufficient amount of DNA template that could be used to effectively detect the presence of a nick in DNA to be contacted with the DsbA protein.

8. Claims 8-9 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gansz in view of Natesan (U.S. Patent No. 6,015,709)

Gansz teaches methods for analyzing transcriptional activity. The reference teaches that binding of the DsbA transcription factor to double-stranded DNA enhances transcription activity. At page 428, Gansz states that "binding of the protein is accompanied by nicking of the DNA. These nicks might contribute to activation of the template for late transcription." Gansz (page 432) also teaches footprinting methods for

detecting the presence of a nick in a DNA template wherein the methods comprise providing a DNA template, contacting the template with DsbA protein, and separating the products electrophoretically on a sequencing gel. An autoradiogram was used to reveal the presence of specific nick sites within the DNA template. In the footprinting methods, DNase I is added to control reactions, while no DNase I is added in reactions that assay for DsbA nicking. The reference also teaches methods for detecting the presence of transcription activity resulting from the binding of DsbA to the DNA template. Gansz does not teach immobilizing the DNA template on a chip.

However, Natesan teaches footprinting methods wherein the DNA to be analyzed is immobilized onto a solid support, such as a chip (see column 21). Natesan teaches that when DNA is immobilized onto a solid support the footprinting assays can be performed using a BIAcore instrument which allows for a more precise analysis of protein binding.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Gansz so as to have immobilized the DNA template on a chip in order to have provided the benefit of allowing for the simultaneous and rapid analysis of multiple DNA templates and to have provided a more accurate means for analyzing DsbA binding to DNA templates.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)-272-0782.

Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Carla Myers
June 7, 2004

CARLA J. MYERS
PRIMARY EXAMINER